Warsaw, July 18, 2013

European Commission

Directorate General for Health and Consumers, Unit SANCO/D/6

Brussels, Belgium

and

European Medicines Agency

London, United Kingdom

Ref. Revision of EU Commission guidelines on Good Manufacturing Practice Medicinal Products – chapters 5 "Production" and 6 "Quality control"

Dear Sir or Madam,

SciencePharma welcomes the Commission's initiative to consult with stakeholders drafts of the revised chapters of the GMP guidelines and appreciates the possibility to provide its comments.

SciencePharma is a Polish consultancy company offering comprehensive regulatory services to the pharmaceutical industry. SciencePharma falls within the EU definition of a small and medium-sized enterprise.

Chapter 5: Production

- Section 5.17 of the draft specifies (in comparison to the current version) that the production of non-medicinal products could be allowed in areas and with the equipment destined for the production of medicinal products "in exceptional circumstances" only. This is not considered to reflect the current practice as significant number of manufacturers produce such products as food supplements, medical devices or cosmetics using the same area / equipment as for used for the production of medicinal products. Moreover, such practices seem to be well justified provided that relevant measures to prevent cross contamination with medicinal products are applied.

  Proposed change:

  5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products but ~~in exceptional circumstances~~ could be allowed where the measures to prevent cross contamination with medicinal products described below and in Chapter 3 can be applied. The production of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

- Proposed changes to examples of technical and organisational measures to mitigate risks of cross-contamination given in section 5.20:

  • *self-contained production areas having* *if necessary* *separate processing equipment and separate HVAC systems. It may also be desirable to isolate certain utilities from those used in other areas*

  • ~~*Dedicating the whole manufacturing facility or a self contained*~~ *production* ~~*area*~~ *on a campaign basis (*~~*dedicated by*~~ *separation in time) followed by a cleaning process of validated effectiveness* (a change to refer only to organisational measures is proposed; moreover not necessarily "whole" manufacturing facility has to be dedicated)

  New section 5.27 of the draft concerns *i.a.* the supply chain traceability for active substances. It is specified that this traceability should include active substance starting materials. This seems not to be well justified as according to art. 46 point (f) of the directive 2001/83/EC (as amended by directive 2011/62/EU) manufacturing authorization holders are obliged to comply with good manufacturing practices and good distribution practices for active substances. It is not explicitly required that supply chain traceability should – as the draft suggests – extend to active substance starting materials. It should be also stressed that manufactures of finished products often have limited data on supply chain of active substance starting materials as sources of these materials are frequently provided only in restricted parts of AMSF / DMF (most often not available to finished product manufacturers).

  As for excipients the attention not necessarily has to be similar as for active substances. It is proposed to consider the following wording:

  Excipients which are considered to pose a particular risk to the quality of the medicinal product, based on formalised quality risk management, should be given ~~*similar*~~ *adequate attention* ~~*to those for active substances*~~ *commensurate with the risks.*

- New section 5.33 of the draft deals with control of starting and packaging materials.

  General comment

  Although it is fully agreed that testing of starting and packaging materials is an essential activity to assure adequate quality, safety and efficacy of finished products, full analyses of these materials do not seem to be feasible and necessary in all cases (and for all tests). It shall be underlined that in particular for excipients and packaging materials significant number of analyses are highly specific and requiring specialised equipment. It should be also noted that for many excipients or packaging materials potential deviation in respect to some functionality-related characteristics may also be detected at the level of the finished drug product (*e.g.* in the course of dissolution testing).

  Hence, it is proposed that any reduction of testing shall take place based on the outcomes of a relevant risk assessment. In the course of such assessment necessity for and extent of in-house full analyses by the finished product manufacturer before reduction and/or periodically should be evaluated.

  Such risk analyses could include, but are not limited to, the following:

  - the nature of the material,
  - range of testing carried out by the manufacturer of the finished product with particular attention to the range of in-house testing reduction,
  - the nature, complexity and criticality of tests for which in-house testing reduction is considered,
  - potential impact on the finished product quality, safety or efficacy of an incompliance in respect to tests for which in-house testing reduction is considered,

- probability of detection of an incompliance at the level of the finished product (*e.g.* some quality defects of excipients may affect dissolution),
- experience in dealing with the manufacturer and/or testing site of the starting or packaging material, including assessment of batches previously received and the history of compliance (of the material in question or other representative materials),
- outcome of any audit at the manufacturing and/or testing site (if conducted),
- any official documents certifying compliance of the manufacturer and/or testing site of the starting or packaging material with relevant good manufacturing practices.

Specific comments:

- In point a) it is specified that a formal agreement should be signed, according to chapter 7, focused in particular on responsibilities related to the distribution conditions. These conditions are likely to be assured more by a supplier (*e.g.* a distributor) of the material and hence the agreement covering the distribution issues should rather be concluded with this entity, if different from the manufacturer.
- Requirement for audits "at the site(s)" carrying out the testing (planned in point b)) is not considered to be justified. Above all it should be noted that the directive 2001/83/EC (as amended) requires audits at active substance manufacturing sites only. Moreover, it is acknowledged that compliance with GMP and reliability of results provided by starting materials manufacturers may be verified in alternative ways. Hence it is proposed to define that the level of supervision (including – if necessary – audits) should be established based on relevant risk analyses.
- Point c) is proposed to be changed (for consistency with section 5.26):

  c) The certificate of analysis provided by the starting material manufacturer should be signed by a designated person with appropriate qualifications and experience. This person should ensure that each batch has been manufactured and checked for compliance with the requirements of the formal agreement or specification.
- In point d) it is proposed to clearly state that reduction of in-house testing may be implemented under condition that a finished product manufacturer has a significant experience in dealing with the starting material manufacturer (not necessarily in respect to the material in question). As for point e) it is proposed to state that necessity for and – if applicable – intervals of full analyses should be determined based on a relevant risk analysis (see the general comment above).

  d) The ~~finished product manufacturer should have a significant experience in dealing with the starting material manufacturer including assessment of batches previously received and the history of compliance before reducing~~ outcome of the quality risk management process should be the basis for justifying the extent to which in-house testing may be reduced. Any significant change in the manufacturing or testing processes should be considered.

  e) Necessity for and – if applicable – intervals at which the finished product manufacturer should ~~also~~ perform a full analysis ~~at appropriate intervals and~~ to compare the results with the supplier's certificate of analysis in order to check the reliability of the latter shall be determined after evaluation of the risks involved. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificate of analysis from the supplier should be discontinued until these measures are completed.
- Note 2 does not seem to be necessary as identification is already discussed in the first paragraph of the section 5.33.

- Section 5.68 is proposed to be changed:

  5.68 "The holder of a marketing authorisation for a medicinal product should, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products[1]. The marketing authorisation holder should be informed by the manufacturer in a timely manner in case of any constraints in manufacturing operations which may result in an abnormal restriction in the supply of a medicinal product. The holder should also notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product[2].

Chapter 6: Quality control

- Section 6.7 is proposed to be changed:

  • a procedure for the investigation of Out Of Specification ~~and anomalous results~~ and Out Of Trend results;

- Section 6.7 is proposed to be changed:

  6.20 Reference standards should be certified, qualified and verified as suitable for ~~its~~ their intended use.

  This section is also proposed to be precised to reflect the issue of compendial standards that should be considered to be suitable for use according to the monograph.

We hope that you will find our comments constructive. We remain at your disposal, should you need further clarification.

Yours faithfully,

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